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Efficacy and Safety of Dapagliflozin in Patients With Acute Heart Failure

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ABSTRACT

BACKGROUND The primary goals during acute heart failure (AHF) hospitalization are decongestion and guideline-directed medical therapy (GDMT) optimization. Unlike diuretics or other GDMT, early dapagliflozin initiation could achieve both AHF goals.

OBJECTIVES The authors aimed to assess the diuretic efficacy and safety of early dapagliflozin initiation in AHF.

METHODS In a multicenter, open-label study, 240 patients were randomized within 24 hours of hospital presentation for hypervolemic AHF to dapagliflozin 10 mg once daily or structured usual care with protocolized diuretic titration until day 5 or hospital discharge. The primary outcome, diuretic efficiency expressed as cumulative weight change per cumulative loop diuretic dose, was compared across treatment assignment using a proportional odds model adjusted for baseline weight. Secondary and safety outcomes were adjudicated by a blinded committee.

RESULTS For diuretic efficiency, there was no difference between dapagliflozin and usual care (OR: 0.65; 95% CI: 0.41-1.02; $P = 0.06$). Dapagliflozin was associated with reduced loop diuretic doses (560 mg [Q1-Q3: 260-1,150 mg] vs 800 mg [Q1-Q3: 380-1,715 mg]; $P = 0.006$) and fewer intravenous diuretic up-titrations ($P \leq 0.05$) to achieve equivalent weight loss as usual care. Early dapagliflozin initiation did not increase diabetic, renal, or cardiovascular safety events. Dapagliflozin was associated with improved median 24-hour natriuresis ($P = 0.03$) and urine output ($P = 0.005$), expediting hospital discharge over the study period.

CONCLUSIONS Early dapagliflozin during AHF hospitalization is safe and fulfills a component of GDMT optimization. Dapagliflozin was not associated with a statistically significant reduction in weight-based diuretic efficiency but was associated with evidence for enhanced diuresis among patients with AHF. (Efficacy and Safety of Dapagliflozin in Acute Heart Failure [DICTATE-AHF]; NCT04298229) (J Am Coll Cardiol 2024;83:1295-1306) © 2024 by the American College of Cardiology Foundation.

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SHOUT
SHARE
IT

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

CEC = Clinical Endpoint Committee

eGFR = estimated glomerular filtration rate

GDMT = guideline-directed medical therapy

HF = heart failure

IV = intravenous

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SGLT2i = sodium glucose co-transporter 2 inhibitor

The 2 primary therapeutic goals during acute heart failure (AHF) hospitalization are complete decongestion and optimization of guideline-directed medical therapy (GDMT) before discharge.[1-3] Studies of loop diuretics combined with either acetazolamide or hydrochlorothiazide demonstrated improved decongestion, but these diuretic combinations do not inherently optimize GDMT and failed to improve postdischarge outcomes.[4,5]

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Early addition of sodium glucose co-transporter 2 inhibitor (SGLT2i) is a potential strategy to achieve both primary AHF therapeutic goals, but the acute efficacy and safety of this strategy are unknown.[1,2] Larger SGLT2i trials randomized patients at the end of hospitalization and evaluated safety and efficacy across intermediate to long-term postdischarge outcomes but not in-hospital safety outcomes, natriuresis, or decongestion.[6,7] Early, smaller studies of SGLT2i in AHF reported increased urine output but lacked protocolized loop diuretic regimens between treatment arms or larger populations for safety assessment.[8,9] Thus, concerns persist regarding the safety and immediate benefits of SGLT2i initiation before patient stabilization during AHF hospitalization. Endocrinology guidelines and international diabetes experts recommend against the routine use of SGLT2i during hospitalization, citing concerns about increased risks of genitourinary infections, ketoacidosis, and acute kidney injury.[10-12] These concerns may explain, at least in part, why only 20% of patients hospitalized for AHF without contraindications are prescribed SGLT2i despite efforts to improve GDMT optimization during AHF hospitalization.[13] We evaluated dapagliflozin initiated within 24 hours of hospital presentation for hypervolemic AHF to assess its safety and additive diuretic benefits to protocolized loop diuretic therapy in DICTATE-AHF (Efficacy and Safety of Dapagliflozin in Acute Heart Failure).

METHODS

TRIAL DESIGN. We conducted an investigator-initiated, multicenter, prospective, randomized, open-label study at 6 hospitals in the United States with objective efficacy outcomes and blinded assessment of safety outcomes. Details regarding the trial design and rationale have been previously published.[14] Although dapagliflozin has not increased hypoglycemic events in outpatients, we adopted an open-label design to facilitate appropriate use of inpatient insulin therapies with dapagliflozin given the well-established elevated hypoglycemia risk during hospitalization.[10-12] The trial protocol and statistical analysis plan are available in the Supplemental Appendix. The study protocol was approved by each Institutional Review Board. All patients provided written informed consent before any study procedures. An independent Data and Safety Monitoring Board reviewed the trial protocol and interim safety analysis. A blinded Clinical Endpoint Committee (CEC) adjudicated prespecified secondary and safety outcomes (Supplemental Appendix).

PATIENTS. Beginning in April 2020, adult patients with type 2 diabetes and an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m^2 admitted to the hospital with AHF and current or planned treatment with intravenous (IV) loop diuretics were eligible for participation. Additional inclusion criteria included at least 2 objective measures of hypervolemia and randomization within 24 hours of presentation to the emergency department or direct admission to the hospital. In September 2021, the protocol was amended to allow enrollment of patients with or without type 2 diabetes and decrease the eGFR inclusion criterion to 25 mL/min/1.73 m^2 because of the publication of new safety data.[15] The main exclusion criteria were type 1 diabetes, systolic blood pressure of <90 mm Hg, serum glucose of <80 mg/dL, or a history of diabetic ketoacidosis. Full inclusion and exclusion criteria are shown in Supplemental Table 1.

RANDOMIZATION AND STUDY PROCEDURES. Within 24 hours of hospital presentation, patients were randomly assigned to either dapagliflozin 10 mg once daily or structured usual care. The Research Electronic Data Capture randomization module was used to randomize patients using permuted blocks of 4 stratified by site.[16]

At randomization, natriuretic peptide concentration, standing weight, and congestion assessment using a validated orthoedema scale assessed by a study physician blinded to treatment assignment were performed.[17] Daily weight measurements used the same standing scale to minimize measurement variation. Patients received a sodium-restricted diet (2 g/d) and a 2,000-mL/d fluid restriction.

An IV loop diuretic titration protocol targeting a urine output of 3 to 5 L/d was used for both study arms to standardize diuretic therapy and prevent empiric IV diuretic changes given the open-label design (Supplemental Table 2). If no IV diuretics were administered before randomization, the initial

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IV loop regimen was 2 to 2.5 times the home diuretic divided into twice daily administration. If IV diuretics were administered before randomization, the treating provider could use the previous diuretic response to guide the initial loop diuretic dose selection. Subsequently throughout the study, loop diuretic doses were titrated every 12 to 24 hours to a dose of at least 960 mg/d of IV furosemide equivalents before a thiazide diuretic was added. Use of nonstudy diuretic therapies including mineralocorticoid receptor antagonist doses of ≥100 mg/d (GDMT doses were allowed), nonstudy thiazides (excluding hydrochlorothiazide of ≤12.5 mg), or acetazolamide were considered a protocol deviation. For patients with type 2 diabetes, endocrinology was consulted, and a standardized protocol was used for in-hospital glycemic control throughout the study (Supplemental Table 3). All other medication changes were at the discretion of the treating team.

A spot urine sample was collected after the initial IV loop diuretic dose, but before dapagliflozin administration, to measure baseline diuretic-induced urine chemistries. On study day 2, a spot urine sample was collected after a loop diuretic dose and after dapagliflozin administration in the intervention arm to measure urine chemistries reflecting combination therapy. A 24-hour urine collection was also completed on day 2 for measuring 24-hour natriuresis and urine volume.

At day 5 or discharge, whichever came first, natriuretic peptide concentration, final standing weight, and a congestion assessment via an orthoedema scale by a study physician blinded to treatment assignment were performed. After hospital discharge, patients were contacted via telephone to assess 30-day postdischarge outcomes.

STUDY OUTCOMES. The primary outcome was diuretic efficiency calculated as the cumulative change in weight per cumulative loop diuretic dose (IV and oral) from enrollment to day 5 or discharge, if sooner. The primary outcome is expressed as kg/40 mg IV furosemide equivalents.[18,19] Diuretic efficiency is independently associated with prognosis and quantifies diuretic response relative to the loop diuretic requirement to account for titration over the study.[5,8,9,18,19]

Secondary outcomes, adjudicated by a blinded CEC, included inpatient worsening heart failure (HF) and 30-day hospital readmission for HF or diabetes-related issues as defined in the Supplemental Appendix. Safety outcomes included change in eGFR from baseline and the following events adjudicated by a blinded CEC: prolonged hospitalization for hypotension or hypoglycemia, ketoacidosis, and inpatient mortality. Exploratory endpoints included changes in natriuretic peptides, serum potassium, measures of natriuresis and diuresis, blinded physician congestion score, and hospital length of stay. We evaluated the cumulative incidence of hospital discharge and duration of IV diuresis during the study period, treating death as a competing risk, as post hoc analyses to understand how dapagliflozin affected these components of length of stay.

Adverse events were collected through 30 days postdischarge. Mild hypoglycemia was defined as serum glucose of 54 to 69 mg/dL and severe hypoglycemia as a serum glucose of <54 mg/dL.[10] Hypotension was defined as either: 1) systolic blood pressure of <90 mm Hg sustained for at least 30 minutes; or 2) symptomatic hypotension necessitating IV fluid or vasopressor therapies. Hypovolemic hypotension was defined as a systolic blood pressure of <90 mm Hg requiring IV fluid administration for hypovolemia.

STATISTICAL ANALYSIS. The prespecified statistical analysis plan is available in the Supplemental Appendix, and details of the study design have been previously published.[14] Assuming a normally distributed standard deviation within each arm of 0.25 kg/40 mg IV furosemide,[8,14] we calculated that a sample size of 120 experimental subjects and 120 control subjects would have 87% power to detect a probability of 0.611 that an observation in the dapagliflozin arm is less than usual care with a 0.05 2-sided significance level. The primary, secondary, and safety outcomes were analyzed according to the intent-to-treat principle, including all randomized patients who either received dapagliflozin or had baseline weight measured in usual care. *P* values and 95% CIs were not adjusted for multiplicity. Participant characteristics were summarized using median (Q1-Q3) or frequency (percentage), as appropriate. The primary outcome was compared across treatment assignment using a proportional odds regression model adjusted for baseline weight. Baseline weight was fit with restricted cubic splines (3 knots) to relax the linearity assumptions. ORs and estimated means were reported. Measures of diuresis and natriuresis were compared across treatment assignment using Wilcoxon rank sum tests. The association of N-terminal pro-B-type natriuretic peptide (NT-proBNP) at discharge with treatment arm was modeled using a proportional odds regression model adjusted for baseline NT-proBNP fit with restricted cubic splines (3 knots). Similarly, the association of discharge eGFR

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TABLE 1 Baseline Characteristics

	Dapagliflozin (n = 119)	Usual Care (n = 119)
Age, y	65 (56-73)	64 (55-74)
Male	78 (66)	67 (56)
Race		
White	79 (66)	84 (71)
Black	39 (33)	29 (34)
Medical history		
History of heart failure	102 (86)	103 (87)
T2DM	84 (71)	85 (71)
Atrial fibrillation or flutter	50 (42)	49 (41)
Heart failure characteristics		
LVEF, %	45 (26-56)	35 (25-60)
LVEF ≤40%	53 (48)	62 (55)
LVEF 41%-49%	10 (9)	3 (3)
LVEF ≥50%	47 (43)	48 (42)
Vital signs		
Systolic blood pressure, mm Hg	121 (112-136)	120 (110-136)
Serum laboratory values		
Sodium, mEq/L	140 (138-141)	139 (137-141)
Potassium, mEq/L	3.9 (3.7-4.3)	3.9 (3.6-4.3)
BUN, mg/dL	23 (17-33)	21 (16-32)
eGFR, mL/min/1.73 m^2	51 (43-68)	54 (40-71)
NT-proBNP, pg/mL	2,277 (1,007-6,670)	2,927 (1,167-5,477)
Glucose, mg/dL	121 (102-152)	126 (101-175)
Hemoglobin A_{1C}, %	6.7 (6.0-8.1)	6.7 (6.0-7.9)
In-hospital medications at randomization		
Beta blocker	68 (58)	73 (62)
ACEI/ARB/ARNI	59 (50)	64 (54)
ARNI	26 (22)	19 (16)
Mineralocorticoid antagonist	55 (46)	66 (55)
Daily dose, mg	25 (25-25)	25 (25-25)
IV loop diuretic bolus dose before randomization	116 (97)	113 (95)
Prerandomization IV loop diuretic dose in FE (mg)	80 (40-160)	80 (80-120)
IV loop diuretic continuous infusion before randomization	13 (11)	13 (11)
Prerandomization IV loop diuretic infusion rate in FE, mg/h	40 (20-80)	40 (20-120)
Insulin, scheduled	66 (55)	63 (53)
Congestion assessment		
Orthoedema score	2 (1.5-3)	2 (2-3)
Edema	108 (91)	106 (89)
Weight gain of ≥5 lb	80 (67)	86 (72)

Values are median (Q1-Q3) or n (%).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; FE = furosemide equivalents in milligrams; IV = intravenous; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; T2DM = type 2 diabetes mellitus.

with treatment arm was modeled using a proportional odds regression model adjusted for baseline eGFR fit with restricted cubic splines (3 knots). Missing data were multiply imputed using predictive mean matching with 20 imputation replications. Statistical analyses were performed using R statistical software (R Core Team).[20] All tests were 2-sided with an alpha level of 0.05.

RESULTS

Between April 2020 and May 2023, 3,672 patients were screened, and 240 were randomized to either dapagliflozin or structured usual care at 6 sites. Two patients were withdrawn (usual care arm: n = 1, unable to stand for weights; dapagliflozin arm: n = 1, treating physician's decision to avoid SGLT2i therapy), leaving 238 patients eligible for analysis (Supplemental Figure 1). Baseline characteristics were balanced between treatment arms (**Table 1**, Supplemental Table 4). Type 2 diabetes was present in 71% of patients, and 52% had a left ventricular ejection fraction of ≤40%. Baseline and daily IV loop diuretic doses with daily IV diuretic titrations are presented in Supplemental Table 5.

PRIMARY OUTCOME. After adjustment for baseline weight, there was no difference in the OR for improved diuretic efficiency between dapagliflozin and usual care (OR: 0.65; 95% CI: 0.41-1.02; $P = 0.06$) (**Table 2**). Model-based estimates of the mean diuretic efficiency were -0.42 kg/40 mg IV furosemide (95% CI: -0.52 to -0.33 kg/40 mg IV furosemide) with dapagliflozin and -0.31 kg/40 mg IV furosemide (95% CI: -0.39 to -0.23 kg/40 mg IV furosemide) with usual care. If this difference was significant, a difference of 0.11 kg/40 mg IV furosemide would translate to an additional weight loss of 1.5 kg for the median furosemide cumulative dose (560 mg) over the study period. Distribution of the primary outcome is shown in Supplemental Figure 2. For the components of the primary outcome, the addition of dapagliflozin to IV loop diuretics resulted in equivalent cumulative weight change (-4.0 kg [Q1-Q3: -6.9 to -1.5 kg] vs -4.2 kg [Q1-Q3: -6.5 to -1.8 kg]; $P = 1.00$) as usual care, but the dapagliflozin arm required significantly less loop diuretic (560 mg [Q1-Q3: 260-1,150 mg] vs 800 mg [Q1-Q3: 380-1,715 mg]; $P = 0.006$) to achieve this weight loss (**Figure 1**). In compliance with the diuresis-guided IV loop diuretic titration protocol, providers did not empirically down-titrate the IV loop diuretic regimen when dapagliflozin was initiated, but rather, dapagliflozin significantly reduced the need for daily IV loop diuretic up-titrations for low urine output per the diuretic protocol (Supplemental Table 5). The effect of dapagliflozin on the primary outcome was generally consistent across prespecified subgroups (**Figure 2**). We did not observe a statistically significant interaction between baseline eGFR and the primary outcome between treatment arms (P for interaction = 0.08).

MEASURES OF DIURESIS AND NATRIURESIS. Among the 176 patients with a complete 24-hour urine

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TABLE 2 Primary, Secondary, Safety, and Exploratory Outcomes and Adverse Events

	Dapagliflozin (n = 118)	Usual Care (n = 116)	Treatment Effect (95% CI)	*P* Value
Primary outcome				
Change in weight (kg)/40 mg IV furosemide, adjusted for baseline weight	-0.42 (-0.52 to -0.33)	-0.31 (-0.39 to -0.23)	0.65 (0.41-1.02)	0.06
Change in weight (kg)/40 mg IV furosemide, unadjusted	-0.24 (-0.53 to -0.08)	-0.16 (-0.35 to -0.07)	0.64 (0.41-1.00)	0.05
Secondary outcomes				
In-hospital worsening heart failure	4	3	–	0.70
30-day hospital readmission for AHF or diabetes-related reasons	7	8	–	0.79
AHF-related readmission	6	8	–	0.58
Diabetes-related readmission	1	0	–	–
Safety outcomes				
Change in eGFR at end of study, mL/min/1.73 m^2	-2.0	-3.2	1.06 (0.68-1.65)	0.79
Ketoacidosis	0	0	–	–
Hypovolemic hypotension	0	1	–	–
Inpatient death	1	5	–	0.10
HF-related death	1	4	–	0.18
Select exploratory outcomes				
NT-proBNP at end-of-study, pg/mL	964 (357-2,490)	1,507 (476-2,834)	0.80 (0.49-1.32)	0.29
Length of stay, d	5.0 (3.2-8.7)	6.2 (3.9-8.7)	–	0.23
All-cause 30-day hospital readmission	19	20	–	0.35
Select adverse events during treatment				
Hypoglycemia	7	9	–	–
Mild: serum glucose 54-69 mg/dL	4	7	–	–
Moderate to severe: serum glucose <54 mg/dL	3	2	–	–
Prolonged hospitalization for hypoglycemia	0	0	–	–
Symptomatic hypotension	2	4	–	–
Prolonged hospitalization for hypotension	1	1	–	–
Acute kidney injury: stage 2	2	0	–	–
Acute kidney injury: stage 3	2	1	–	–
Genitourinary tract infections	0	1	–	–
Serum potassium <3.0 mEq/L	1	1	–	–

Values are median (Q1-Q3) or n, unless otherwise indicated. Treatment effect is presented as OR. All *P* values, except the primary endpoint, are descriptive because no corrections for multiple testing were prespecified.

AHF = acute heart failure; HF = heart failure; other abbreviations as in Table 1.

collection on day 2, patients excreted a median of 262 mmoL of sodium (Q1-Q3: 156-378 mmoL) and 2,952 mL of urine (Q1-Q3: 2,094-3,974 mL). Dapagliflozin increased 24-hour measured natriuresis compared with usual care (median: 50 mmoL sodium/40 mg IV furosemide [Q1-Q3: 24-102 mmoL sodium/40 mg IV furosemide] vs 35 mmoL sodium/40 mg IV furosemide [Q1-Q3: 19-63 mmoL sodium/40 mg IV furosemide]; $P = 0.025$) (**Figure 3A**). Stated differently, the usual care arm required an additional 80 mg of IV furosemide to achieve equivalent 24-hour natriuresis as the dapagliflozin arm (Supplemental Table 6). Dapagliflozin significantly increased 24-hour urine output (median: 634 mL/40 mg IV furosemide [Q1-Q3: 333-1,275 mL/40 mg IV furosemide vs 403 mL/40 mg IV furosemide [Q1-Q3: 249-750 mL/40 mg IV furosemide]; $P = 0.005$) (**Figure 3B**). Urine sodium concentration and fractional excretion of sodium per 40 mg IV furosemide in spot urine samples did not differ between treatment arms (Supplemental Table 6).

DECONGESTION AND HOSPITAL DISCHARGE. In exploratory analyses treating death as a competing risk, dapagliflozin reduced both the time to complete IV diuretic therapy ($P = 0.003$) (Supplemental Figure 3) and the time to hospital discharge (52% vs 33% patients discharged by day 5; $P = 0.007$) (**Figure 3C**). Despite an observed difference during the study period, total length of stay including days after the end of the study was not statistically different (**Table 2**). Although the usual care arm received IV diuretics for more time, the dapagliflozin arm had a nonsignificant improvement in orthoedema score at the end of the study (OR: 0.66; 95% CI: 0.38-1.13) (Supplemental Figure 4). NT-proBNP decreased substantially in both the dapagliflozin (median: 47%

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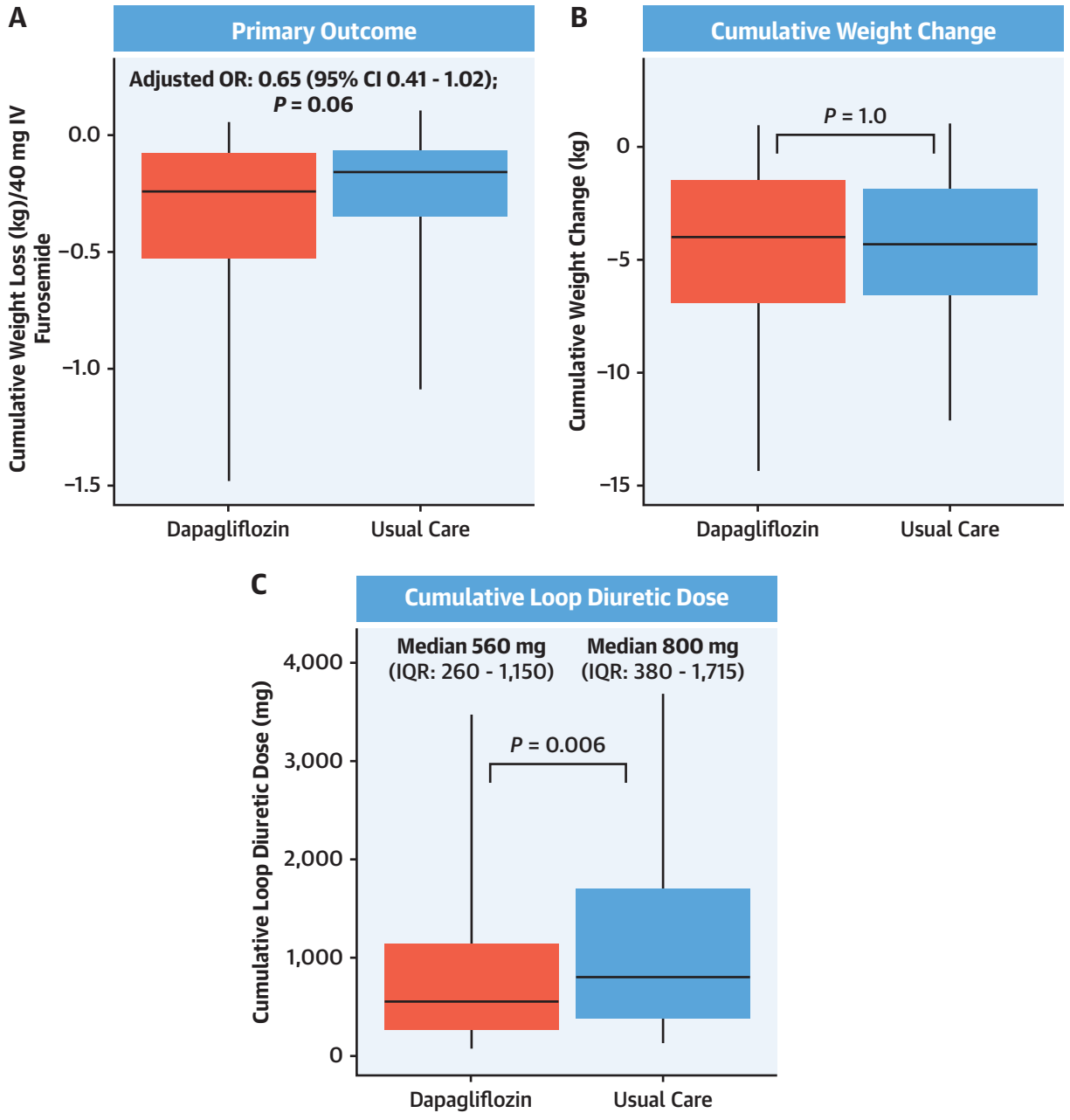
FIGURE 1 Primary Outcome and Components



(A) The odds of a favorable primary outcome expressed as weight change per 40 mg of IV furosemide adjusted for baseline weight failed was neutral. The components of the primary outcome—(B) cumulative weight change and (C) cumulative loop diuretic dose—are presented as median (IQR), with whiskers representing 5th to 95th percentiles. Dapagliflozin significantly reduced the cumulative loop diuretic dose required to achieve an equivalent weight change compared with structured usual care. IV = intravenous.

reduction) and usual care (median: 43% reduction) arms by the end of the study (Table 2). Patients randomized to early dapagliflozin were more likely to be on an SGLT2i at hospital discharge (P = 0.006) (Supplemental Table 7).

ADVERSE EVENTS. Early dapagliflozin initiation did not increase the risk of in-hospital worsening HF or 30-day readmissions for either HF or diabetes-related reasons compared to usual care (Table 2). No patient experienced ketoacidosis. The change in eGFR from

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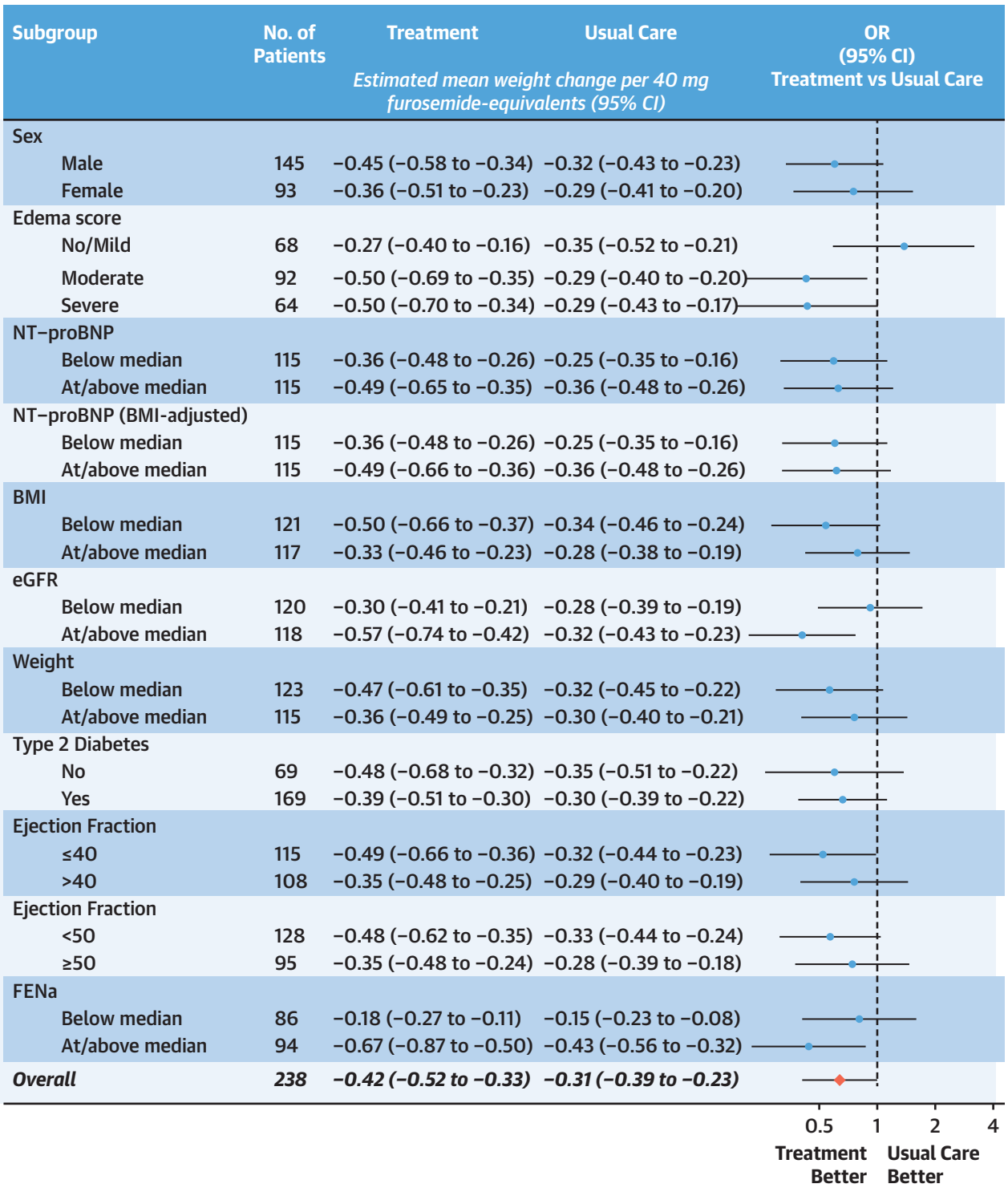
FIGURE 2 Heterogenicity of Treatment Effect Forest Plot


Subgroup
No. of Patients
Treatment
Usual Care
Estimated mean weight change per 40 mg furosemide-equivalents (95% CI)
OR (95% CI) Treatment vs Usual Care
Sex
Male 145 −0.45 (−0.58 to −0.34) −0.32 (−0.43 to −0.23)
Female 93 −0.36 (−0.51 to −0.23) −0.29 (−0.41 to −0.20)
Edema score
No/Mild 68 −0.27 (−0.40 to −0.16) −0.35 (−0.52 to −0.21)
Moderate 92 −0.50 (−0.69 to −0.35) −0.29 (−0.40 to −0.20)
Severe 64 −0.50 (−0.70 to −0.34) −0.29 (−0.43 to −0.17)
NT−proBNP
Below median 115 −0.36 (−0.48 to −0.26) −0.25 (−0.35 to −0.16)
At/above median 115 −0.49 (−0.65 to −0.35) −0.36 (−0.48 to −0.26)
NT−proBNP (BMI-adjusted)
Below median 115 −0.36 (−0.48 to −0.26) −0.25 (−0.35 to −0.16)
At/above median 115 −0.49 (−0.66 to −0.36) −0.36 (−0.48 to −0.26)
BMI
Below median 121 −0.50 (−0.66 to −0.37) −0.34 (−0.46 to −0.24)
At/above median 117 −0.33 (−0.46 to −0.23) −0.28 (−0.38 to −0.19)
eGFR
Below median 120 −0.30 (−0.41 to −0.21) −0.28 (−0.39 to −0.19)
At/above median 118 −0.57 (−0.74 to −0.42) −0.32 (−0.43 to −0.23)
Weight
Below median 123 −0.47 (−0.61 to −0.35) −0.32 (−0.45 to −0.22)
At/above median 115 −0.36 (−0.49 to −0.25) −0.30 (−0.40 to −0.21)
Type 2 Diabetes
No 69 −0.48 (−0.68 to −0.32) −0.35 (−0.51 to −0.22)
Yes 169 −0.39 (−0.51 to −0.30) −0.30 (−0.39 to −0.22)
Ejection Fraction
≤40 115 −0.49 (−0.66 to −0.36) −0.32 (−0.44 to −0.23)
>40 108 −0.35 (−0.48 to −0.25) −0.29 (−0.40 to −0.19)
Ejection Fraction
<50 128 −0.48 (−0.62 to −0.35) −0.33 (−0.44 to −0.24)
≥50 95 −0.35 (−0.48 to −0.24) −0.28 (−0.39 to −0.18)
FENa
Below median 86 −0.18 (−0.27 to −0.11) −0.15 (−0.23 to −0.08)
At/above median 94 −0.67 (−0.87 to −0.50) −0.43 (−0.56 to −0.32)
Overall 238 −0.42 (−0.52 to −0.33) −0.31 (−0.39 to −0.23)
0.5
1
2
4
Treatment Better
Usual Care Better

Treatment effect across prespecified subgroups based on the median value at randomization. BMI = body mass index; eGFR = estimated glomerular filtration rate; FENa = fractional excretion of sodium; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

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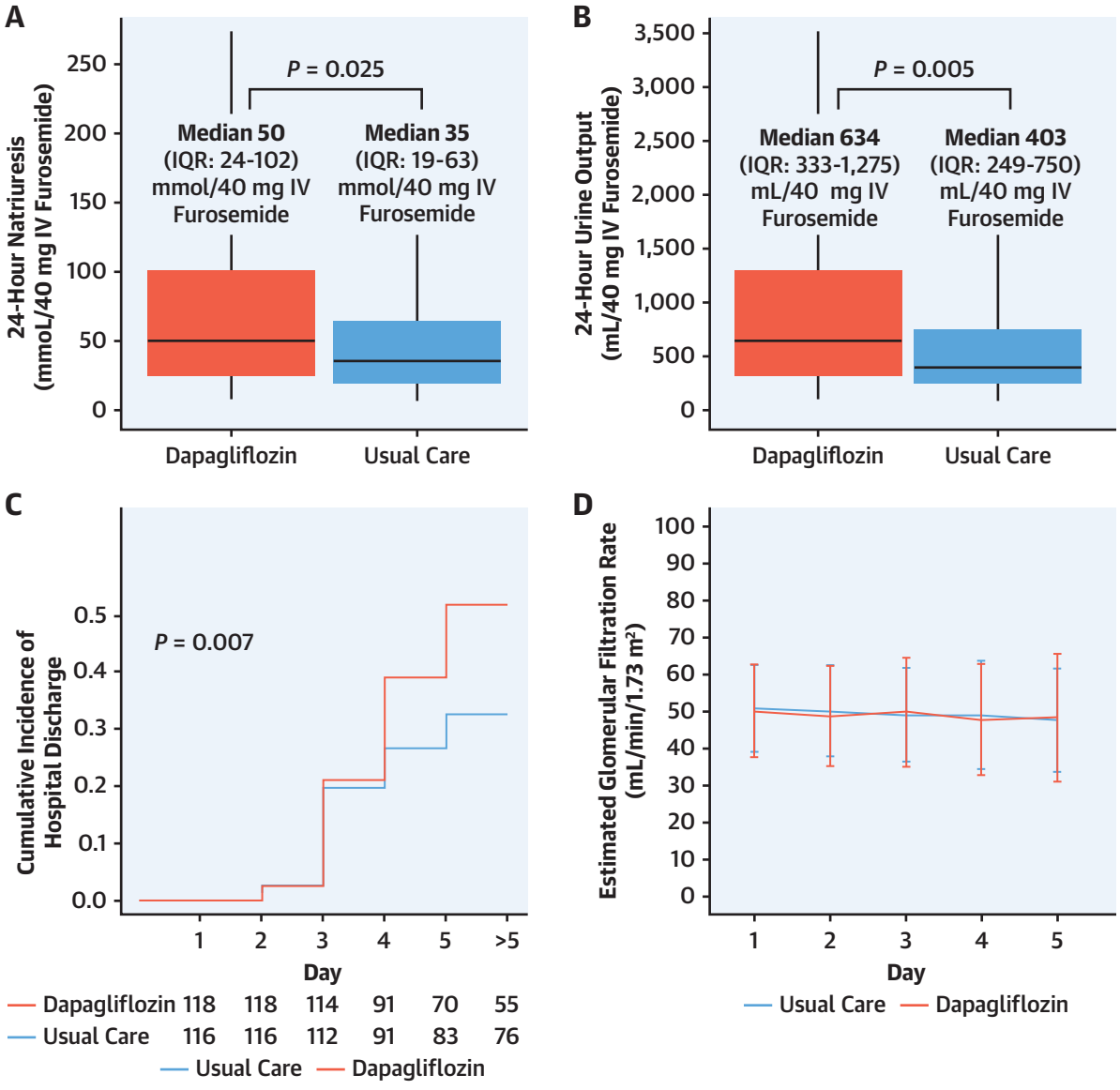
FIGURE 3 Safety and Exploratory Outcomes



Dapagliflozin significantly increased (A) 24-hour natriuresis and (B) 24-hour urine output per 40 mg IV furosemide in the n = 176 patients with a complete 24-hour urine collection on study day 2. Data are presented as median (IQR) with whiskers representing 5th to 95th percentiles. (C) The dapagliflozin arm had a greater probability of hospital discharge during the study period, treating death as a competing risk. (D) The mean ± SD change in estimated glomerular filtration rate did not differ between treatment arms. *P* values are descriptive because no corrections for multiple testing were prespecified. IV = intravenous.

baseline to the end of the study was no different with dapagliflozin than usual care (-2.0 mL/min/1.73 m^2 vs -3.2 mL/min/1.73 m^2; $P = 0.79$) (**Figure 3D**).

The incidence of adverse events was similar between treatment arms (**Table 2**). Adverse events through 30-day follow-up are detailed in Supplemental Table 8, and acute kidney injury events are further described in Supplemental Table 9. Changes in serum chemistries did not differ between treatment arms (Supplemental Table 10).

Dapagliflozin did not increase total or severe hypoglycemia events (**Table 2** and Supplemental Table 11). Mean blood glucose was not different with dapagliflozin relative to usual care for all patients (122 mg/dL [Q1-Q3: 106-147 mg/dL] vs 127 mg/dL [Q1-Q3: 105-152 mg/dL]; $P = 0.49$) or those with type 2

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diabetes (139 mg/dL [Q1-Q3: 116-158 mg/dL] vs 134 mg/dL [Q1-Q3: 120-165 mg/dL]; $P = 0.71$). Among patients with type 2 diabetes, the median daily insulin dose did not differ between dapagliflozin and usual care (9.6 U [Q1-Q3: 2.0-33.5 U] vs 9.3 U [Q1-Q3: 1.2-26.7 U]; $P = 0.72$).

DISCUSSION

In this multicenter, randomized trial with high-dose protocolized IV diuretic therapy titration, we investigated the efficacy and safety of dapagliflozin initiation within 24 hours of hospital presentation for AHF. The central findings are as follows: 1) dapagliflozin achieved equivalent weight reduction with significantly lower loop diuretic cumulative doses and fewer IV diuretic up-titrations required than usual care, resulting in a nonsignificant treatment effect for the primary outcome; 2) early dapagliflozin initiation was safe across all diabetic and cardiorenal in-hospital outcomes; and 3) dapagliflozin significantly increased natriuresis and urine output per 40 mg of IV furosemide. The primary goals of AHF are decongestion and GDMT optimization. The totality of data supports the early initiation of dapagliflozin in AHF to facilitate both these goals (**Central Illustration**).

These observations have important implications for SGLT2i use across the spectrum of HF. First, dapagliflozin demonstrated safety in the present study, which, compared to previous studies, had a larger multicenter population with blinded, standardized adverse event adjudication. Dapagliflozin can be safety started on the first day of AHF hospitalization before patient stabilization, inherently facilitating rapid GDMT optimization. Second, dapagliflozin provided acute diuretic benefits against a background of protocolized, high-dose IV loop diuretics. Dapagliflozin improved multiple measures of diuretic efficacy. The primary outcome of weight-based diuretic efficiency favored dapagliflozin but failed to meet statistical significance. Unlike hard cardiovascular outcomes, diuretic response lacks any one definitive metric; thus, we evaluated several outcomes reflecting diuretic efficiency to ensure a consistent treatment effect.[2,21,22] Dapagliflozin improved natriuresis-based and diuresis-based diuretic efficiency, reduced IV loop diuretic up-titration for poor diuretic response, and shortened the duration of IV diuresis.

Numerous AHF therapies have been investigated with the hope of improving acute decongestion and postdischarge outcomes. Neither dopamine, milrinone, nesiritide, nor high-dose spironolactone increased diuresis or outcomes in AHF.[1,2] Recently, empiric additions of acetazolamide, thiazides, and SGLT2i improved diuresis. Both acetazolamide's and SGLT2i's diuretic effects occur largely by inhibiting renal sodium hydrogen exchanger 3-mediated sodium transport.[4,23-27] Given the potential mechanistic duplication, acetazolamide's additive diuretic effect and clinical utility in patients receiving SGLT2i are unknown.[4,28] Although loop-thiazide combinations increase natriuresis more than SGLT2i-loop combinations, thiazides increase the risk of worsening renal function and severe electrolyte depletion.[5,29] Early addition of SGLT2i in AHF may decrease the need for thiazide addition and avoid these risks. Poor diuretic efficiency is independently associated with several adverse HF outcomes including mortality across multiple AHF cohorts.[18,19] Whether this risk can be mitigated by improving diuretic efficacy is unclear. Increasing decongestion and diuretic efficiency with acetazolamide or thiazides did not improve postdischarge outcomes.[4,5] SGLT2i have convincingly reduced HF hospitalizations and mortality in prior studies, likely via other nondiuretic mechanisms.[1,2,6,7,26] Therefore, DICTATE-AHF was not designed to evaluate improvement in postdischarge outcomes. For these reasons, early SGLT2i initiation should be prioritized over other diuretic combinations.

Our observations build on EMPA-RESPONSE-AHF (n = 80) and EMPAG-HF (Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure) (n = 60), reporting increased diuresis with the addition of SGLT2i to IV loop diuretics in a larger multicenter population.[8,9] The use of a urine output-based IV diuretic titration protocol with a standard net negative goal of 2 to 3 L/d in DICTATE-AHF resulted in a higher median cumulative loop diuretic dose in the comparator group (800 mg IV furosemide) than in EMPA-RESPONSE-AHF (300 mg IV furosemide) and EMPA-AHF (351 mg IV furosemide). Thus, SGLT2i enhances diuresis even when diuretic goals are standardized across treatment arms and diuretic resistance exists. Collectively, these studies indicate that early SGLT2i initiation is safe and provides modest diuretic benefit in AHF.

Safety concerns related to hypoglycemia, ketoacidosis, and changes in renal function have limited SGLT2i use during hospitalization. Endocrinology societies advocate for trials of noninsulin therapies with prespecified glycemic measures in hospitalized patients with diabetes and cardiovascular disease.[10-12] We designed DICTATE-AHF to evaluate in-hospital and postdischarge diabetes-related outcomes. Dapagliflozin did not increase the risk of hypoglycemia, and no patient experienced ketoacidosis during

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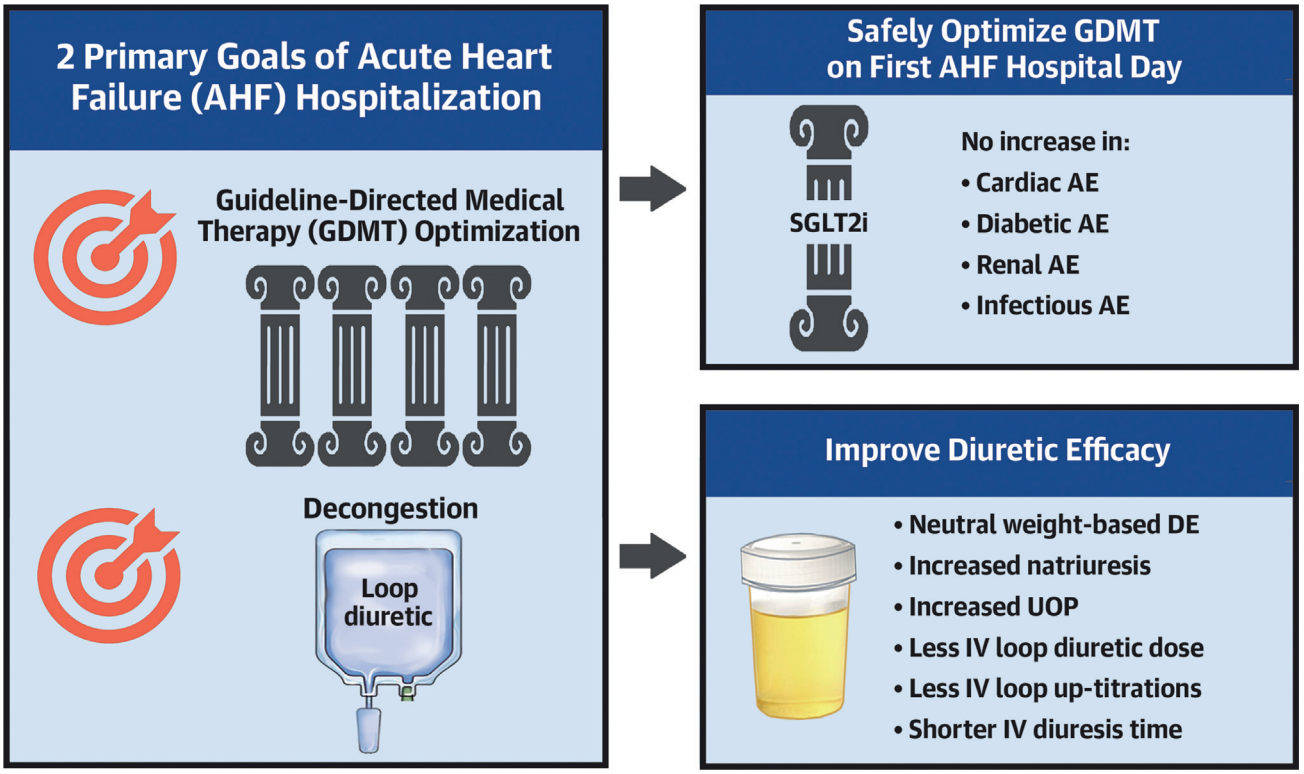
CENTRAL ILLUSTRATION **Efficacy and Safety of Early Dapagliflozin in Acute Heart Failure**



Cox ZL, et al. J Am Coll Cardiol. 2024;83(14):1295–1306.

Early dapagliflozin initiation before patient stabilization on the first day of acute heart failure (AHF) hospitalization was safe, allowing rapid guideline-directed medical therapy (GDMT) optimization. After adjustment for baseline weight, the OR for the primary outcome of diuretic efficiency was neutral for dapagliflozin (OR: 0.65; 95% CI: 0.41-1.02; $P = 0.06$) compared to usual care. However, dapagliflozin improved multiple other measures of diuretic efficacy, with the totality of data suggesting a modest diuretic benefit. AE = adverse event; DE = diuretic efficiency; IV = intravenous; SGLT2i = sodium glucose cotransporter 2 inhibitor; UOP = urine output.

hospitalization. eGFR commonly worsens during aggressive diuresis, and SGLT2i decreases eGFR within the first weeks of therapy.[30,31] However, prior studies of SGLT2i initiation during AHF observed conflicting changes in eGFR.[8,9,32,33] Despite aggressive IV diuresis in DICTATE-AHF, dapagliflozin did not worsen eGFR or cause significant acute kidney injury events (Supplemental Table 8) compared to usual care. Importantly, this was not the result of empiric IV loop diuretic down-titration in the dapagliflozin arm. It may be that the acute, mild changes in eGFR with SGLT2i are obscured by the common underlying fluctuations in eGFR increases and decreases during decongestion in AHF.[30,33,34]

Despite the well-established benefits of SGLT2i in HF and kidney disease, significant implementation gaps exist. Only 20% of SGLT2i candidates hospitalized for AHF are prescribed SGLT2i, and only 12% of patients with chronic kidney disease receive SGLT2i therapy.[13,35] GDMT prescription at hospital discharge significantly increases the likelihood of chronic medication optimization and adherence.[36-39] Our safety findings should encourage early in-hospital use, which can translate into improved chronic SGLT2i prescription, adherence, and long-term benefits.

STUDY LIMITATIONS. The open-label design may have introduced unmeasured bias despite the use of a standardized diuretic titration protocol, objective outcomes, and blinded adjudicators for prespecified subjective assessments. Given the limited experience with in-hospital SGLT2i at the time of study design, this compromise was acceptable to ensure that the hypoglycemia risk was mitigated. Dapagliflozin had a moderate treatment effect but did not reach

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statistical significance, likely because of the moderate sample size. However, the totality of evidence strongly favored dapagliflozin. Less than 10% of patients screened were enrolled; however, this was because all patients presenting with potential AHF during the COVID pandemic were screened to enroll within 24 hours of presentation. One-third of patients with failed screens ultimately did not have AHF (did not require IV diuretics or had end-stage renal disease), and an additional 19% were excluded for absence of type 2 diabetes before the inclusion criteria change. The primary outcome was adjusted for baseline weight as in other AHF trials, but it is unclear whether baseline weight influences the degree of hypervolemia.

CONCLUSIONS

Early initiation of dapagliflozin during AHF hospitalization is safe. Dapagliflozin was not associated with a statistically significant reduction in weight-based diuretic efficiency but was associated with evidence for enhanced diuresis among patients with AHF. Additionally, early dapagliflozin initiation fulfills a component of GDMT optimization, leading to the previously established cardiorenal benefits.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with acute decompensated heart failure, dapagliflozin can be safely initiated on the first day of hospitalization.

TRANSLATIONAL OUTLOOK: Further studies are needed to clarify the additive diuretic benefit of SGLT2i therapy early in the course of hospitalization for patients with acute decompensated heart failure.

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KEY WORDS acute heart failure, dapagliflozin, diuresis, heart failure, SGLT2i

APPENDIX For a list of the DICTATE-AHF Study Group, CEC and adjudication definitions, a description of events for CEC review, and the definitions of CEC blindly adjudicated outcomes, as well as supplemental tables and figures, please see the online version of this paper.

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